Reviewer: S. Semalulu , Date April 10, 2001

STUDY TYPE: Carcinogenicity - mice [feeding]; OPPTS 870.4200 [§83-2]; OECD 451.

TEST MATERIAL (PURITY): SZX 0722 (99.4%) [Iprovalicarb]

SYNONYMS: Melody, Phencaramid

CITATION: K.H. Leser and O. Vogel (1997): SZX 0722 - Oncogenicity Study in B6C3F_1-Mice (administration in the food over 2 years). Bayer AG, Report no. 26450 (July 11, 1997). MRID not available. Unpublished.

SPONSOR: Bayer Corporation.

EXECUTIVE SUMMARY:

In a carcinogenicity study (MRID not available), SZX 0722 technical (95.8 - 98.5 %) was administered to groups of 50 male and 50 female B6C3F_1 mice, in the diet at concentrations of 0, 280, 1400, and 7000 ppm (equal to 0, 58.5, 283.4, and 1566.8 mg/kg bw/day for males and 0, 97.4, 503.1, and 2544.0 mg/kg bw/day for females) for up to 105 weeks. An additional 10 animals/sex/dose were similarly treated to serve as interim sacrifices at 52 weeks. There were no treatment related effects on clinical signs, mortality, body weight, absolute food consumption and water intake. However, relative to body weight gain, food and water intakes of males at 7000 ppm were marginally (5-9%) increased. Absolute body weights of males at 7000 ppm were slightly lower (4.1%) compared to controls, throughout the study. Blood urea concentrations were increased in both sexes at 1400 and 7000 ppm, suggestive of restricted kidney function at these dose levels. Triglyceride concentration was significantly higher in males at 7000 ppm at 52 weeks, but not at the end of the treatment period. At the interim and the final necropsy, male mice at 1400 and 7000 ppm showed lower absolute and relative kidney weights compared to controls. Both absolute and relative liver weights were increased in males at 280 ppm and above, but the increase was not dose-related. The increased absolute and relative liver weights in males at 280 ppm were attributed to the higher incidence of hepatocellular neoplasms at this dose, and not considered treatment-related, because of a lack dose a dose relationship. The increase in liver weights in both sexes at 7000 ppm, was accompanied by histological changes in the tissue and considered toxicologically significant. Increases in the incidences of fatty changes in the liver were observed in male and female mice at 7000 ppm, and were considered treatment-related. At terminal necropsy, the incidence of tubular vacuolization of the kidney was markedly decreased in males at 1400 ppm and above. As the kidney histological changes correlated with decreased kidney weights and increased blood urea concentration at these dose levels, they were deemed to indicate an impairment of kidney function. There was no evidence of treatment-related tumours in either sex at all dose levels.

The LOAEL in both sexes was 1400 ppm (283.4 mg/kg bw/d in males and 503.1 mg/kg bw/d in females), based on increased blood urea concentrations (both sexes) and decreased kidney weights (males), as well as histological kidney changes in males 1400 ppm and above. The NOAEL in both sexes was 280

ppm (58.5 mg/kg bw/day).

SZX 0722 technical was not carcinogenic in mice under the conditions of this study.

This carcinogenicity study in the mouse is acceptable, and satisfies the guideline requirements for a carcinogenicity study (83-2); OECD 451 in mice

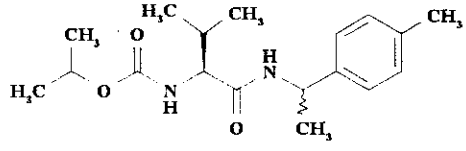
COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided. Animals scheduled for interim necropsy after one year were included in the study (but not examined histopathologically), and supplementary haematological and clinicochemical tests were conducted to detect possible chronic toxicological effects. Those deviations do not alter the acceptability of this study.

I. MATERIALS AND METHODS

A. MATERIALS:

1 **Test Material:** SZX 0722

Description:	Technical, a white powder
Lot/Batch #:	NLL 4812-6.1
Purity:	95.8 -98.5 % a.i.
Compound Stability:	Stable at room temperature
CAS #:	140923-25-7
Structure	



2. **Vehicle and/or positive control:** 1 % (DAB 10) Peanut oil

3 **Test animals:**

Species:	Mice	
Strain:	B6C3F(SPF)	
Age/weight at study initiation:	Young adult, 20-21 g males; 16.6 - 17.2 g females	
Source:	Bomholtgard breeding and Research Centre Ltd. 8680 Ry, Denmark	
Housing:	Individually caged in Type II Macrolon cages, on wood granule bedding during acclimatization and dosing.	
Diet:	Altomin fixed formula standard diet 1321 (Altromin, GmbH, Lage), fed *ad libitum*	
Water:	Tap water in 300 ml polycarbonate bottles, provided *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 2 °C
	Humidity:	55 ± 5 %
	Air changes:	15-20/hr
	Photoperiod:	12 hrs dark/ 12 hrs artificial light
Acclimation period:	1 week	

B. STUDY DESIGN:

1. **In life dates** - Start: January 1994 - February 1996.

2. **Animal Assignment/Dose Levels:** Animals were randomly assigned to the test groups noted in Table 1 (using computer generated random numbers).

TABLE 1: STUDY DESIGN

Test Group	Dose. in Diet (ppm)	Dose to animal (mg/kg bw/d)		# Main Study 24 months (105 weeks)		# Interim Sacrifice 12 months	
		male	female	Male	Female	Male	Female
Control	0	0	0	50	50	10	10
Low (LDT)	280	58.5	97.4	50	50	10	10
Mid (MDT)	1400	283.4	503.1	50	50	10	10
High (HDT)	7000	1566.8	2544	50	50	10	10

3. **Dose Selection:** The doses were selected based on findings from a sub-chronic (13 week) dietary study with SZX 0722 in mice, which indicated altered liver weights occurring in animals fed diets containing 7000 ppm (females) and changes in red blood cell parameters affecting both sexes at 14000 ppm.

4. **Diet preparation and analysis:**

Diets were prepared weekly, by mixing appropriate amounts of test substance with Altromin 1321 Meal and were stored at ambient temperature. To all diet mixtures, peanut oil (10 g/kg food) was added to minimize dust formation. Homogeneity at study commencement, and stability were tested on food samples collected at 13 week intervals. During the study, samples of treated food were analysed for the three nominal concentrations, at 13 week intervals, for stability and concentration.

Results of diet analysis-
Results of the analysis for homogeniety, stability and mean concentration, of the test material in food samples expressed as a percentage of the target concentration were as follows:

Homogeneity Analysis: 91 - 101% of nominal concentration.

Stability Analysis: 101 to 108% of nominal concentration. Stable for up to 14 days

Concentration Analysis: 92 - 105% of nominal concentration

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5.. **Statistics:** Statistical evaluations for clinical chemistry, haematology, body, food water and organ

weights were performed using SAS routines. Statistical significance between control and treated animals was set at $p \leq 0.05$ and $p \leq 0.01$.

C. METHODS:

1. Observations:

Animals were inspected twice daily (once on weekend and holidays) for signs of toxicity and mortality. A detailed physical examination was conducted once weekly. Food and water consumption were measured weekly.

2. Body weight

Animals were weighed weekly.

3. Food consumption and compound intake:

Food consumption for each animal was determined and mean daily diet consumption was calculated as grams of food/kg body weight/day. Food efficiency was calculated as mean food intake per kilogram body weight per day and compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination

Eyes were examined grossly at the beginning and end of the study.

5. Haematology & Clinical Chemistry:

Blood samples from the retro-orbital sinus were collected from 10 animals/sex/dose at 52, 79 and 103 weeks for haematological analyses, or 53 and 104 weeks for clinical chemistry analyses.
The parameters CHECKED (X) in the table below were parameters.

a. Haematology

x	Hematocrit (HCT)	x	Leukocyte differential count
x	Hemoglobin (HGB)	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)	x	Mean corpusc. HGB conc.(MCHC)
x	Erythrocyte count (RBC)	x	Mean corpusc. volume (MCV)
x	Platelet count	x	Reticulocyte count
x	Blood clotting measurements (Thromboplastin time) (Thromboplastin time) (Clotting time) (Prothrombin time)		

b. Clinical Chemistry*

X	**ELECTROLYTES**	X	**OTHER**
x	Calcium	x	Albumin
x	Chloride	x	Creatinine
x	Magnesium	x	Blood urea nitrogen
x	Phosphorus	x	Cholesterol
x	Potassium		Globulins
x	Sodium	x	Glucose
		x	Bilirubin
	ENZYMES	x	Total serum protein (TP)
x	Alkaline phosphatase (ALK)	x	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
x	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
x	Serum alanine amino-transferase (also SGPT)		
	Serum aspartate amino-transferase (also SGOT)		
x	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

* Not required for carcinogenicity studies based on Subdivision F Guidelines.

6. Urinalysis*

Urine was not collected. Therefore, urine parameters were not examined.

	Appearance		Glucose
	Volume		Ketones
	Specific gravity		Bilirubin
	pH		Blood
	Sediment (microscopic)		Nitrate
	Protein		Urobilinogen

* Not required for carcinogenicity studies based on Subdivision F Guidelines.

7. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examination, and the tissues checked (x) below were collected for histological examination In addition, the organs (marked XX) in the table were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
x	Tongue	x	Aorta*	xx	Brain*
x	Salivary glands*	xx	Heart*	x	Peripheral nerve*
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	xx	Spleen*	x	Eyes (optic n.)*
x	Jejunum*	x	Thymus*		
x	Ileum*				GLANDULAR
x	Cecum*		UROGENITAL	x	Adrenal gland*
x	Colon*	xx	Kidneys*+	x	Lacrimal gland
x	Rectum*	x	Urinary bladder*	x	Mammary gland*
xx	Liver*+	xx	Testes*+	x	Parathyroid*++
x	Gall bladder*	x	Epididymides	x	Thyroids*++
x	Pancreas*	x	Prostate		
		x	Seminal vesicle		OTHER
	RESPIRATORY	x	Ovaries*+	x	Bone*
x	Trachea*	x	Uterus*	x	Skeletal muscle*
x	Lung*			x	Skin*
x	Nose			x	All gross lesions and masses*
x	Pharynx				
x	Larynx				

* Required for carcinogenicity studies based on Subdivision F Guidelines.
+ Organ weight required in chronic studies.
++ Organ weight required for non-rodent studies.

II. RESULTS

A. Observations

1. Clinical signs of toxicity -
Daily observations revealed no treatment-related clinical signs, or effects on general behaviour.

2. Mortality -
Cumulative morality determined at 90 day intervals showed that survival rates of treated animals of both sexes in all dose groups were similar to the controls throughout the treatment period. There were no treatment-related effects on mortality.

B. Body weight and body weight gain.
In females of all dose levels, and males treated with up to 1400 ppm, body weight development was comparable to the controls . In males at 7000 ppm, body weights were lower than the control, albeit slightly (maximum 4.1% of control) through most of the study duration. This slight difference in body weight development was not considered biologically significant. Overall, the week 1 to week 104 body weight gain of males at 7000 ppm was lower (12%) than the controls, although the effect dose not appear to be clearly dose-related (Table 2 and Fig 1.).

TABLE 2: Mean body weight gains (BWG) [a] of male animals.

Dose (ppm)	0	280	1400	7000
MALES Initial BW (gm)	20.6	21.4	20.6	20.2
BWG Wk 1 (gm)	0.8	-0.2	0.7	1
BWG Wk 1-13 (gm)	6	7	6.7	5.9
BWG Wk 13-25 (gm)	4.8	5.5	6.7	4.3
BWG Wk 26-53 (gm)	6	4.3	5.9	4.2
BWG Wk 52-73 (gm)	0.5	0.2	0.1	-0.3
BWG Wk 73-105 (gm)	-4.1	-4.2	-4.6	-3.5
Overall BWG Wk 1-104 (gm)	13.2	12.6	15.5	11.6

C. Food consumption and compound intake

1. Food and water consumption

Food intake values are presented in Table 3. Food intake in both sexes did not differ from the controls in a toxicologically relevant manner Absolute water consumption did not differ from control groups. In males at 7000 ppm, the water consumption per kg body weight was slightly higher (+9%) than in controls. The changes in food and water consumption were marginal (not exceeding 10% of the control), and were not considered toxicologically significant.

2. Compound consumption (time-weighted average)

Compound intake is presented in Table 1. In all dose groups of both sexes, the test compound consumption was consistent with the selected dose factor of 5.

3. Food and water efficiency

When food intake was calculated in relation to body weight gained, male animals at 7000 ppm showed slightly increased (5%) food intake per unit weight gained, compared to control. Likewise, in relation to body weight gained, at 7000 ppm, water consumption per unit weight gained was slightly higher (9%) than in controls.

Figure1. Body weights of male animals.

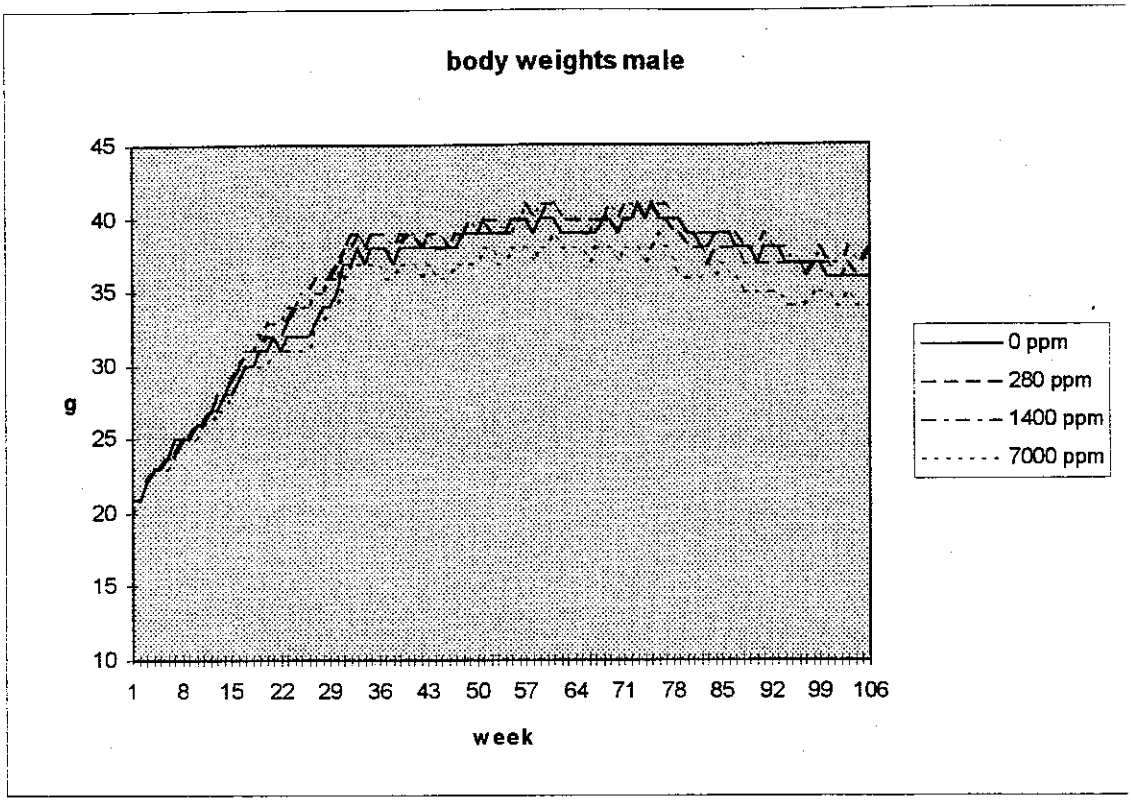


Table 4. Mean Food and water intake per unit body weight gain (food efficiency) and terminal body weight.

Animal sex	Males				Females			
Dose level (ppm)	0	280	1400	7000	0	280	1400	7000
Mean food intake (g/kg bw/day)	212.3	208.9	202.4	223.8	353.8	347.8	359.4	363.4
Mean water intake (g/kg bw/day)	153.0	153.3	152.7	167.2	202.6	193.3	187.4	202.6
Mean terminal body weight. (g) week 105	36.0	35.9	37.5	34.3	29.1	29.9	29.4	28.8

D. Ophthalmoscopic examination -

Opthalmoscopic examinations were not conducted.

E. Blood analyses

1. Haematology

There were no treatment related effects on red blood cell and thrombocyte parameters at all dose levels. Leukocyte counts of males at 7000 ppm were slightly lower than the controls, but were within the historical control range, whereas the mean leucocyte count of control males were consistently at the upper border of the historical control values (Table 5). Therefore, the slight decrease in leukocyte counts of males at 7000 ppm was considered to be incidental.

Table 5. Leucocyte counts of male and female animals at 53 and 104 weeks.

	0 ppm		280 ppm		1400 ppm		7000 ppm	
Week	53	104	53	104	53	104	53	104
Leukocyte counts (10E9/L)								
Males	5.8	6.8	5.1	6	5.6	6.4	3.9	4.1*
Females	4.1	3.6	3	3.5	3.1	3.9	2.9	3.5

* = $p \leq 0.5$

2. Clinical Chemistry -

Clinical chemistry data are presented in Table 6. At week 104, blood urea concentrations were slightly higher in males and females at 1400 and 7000 ppm compared to controls, which was considered indicative of slightly restricted kidney function. Triglyceride concentration was significantly higher in males at 7000 ppm at week 53, although not at the end of the treatment period. The changes in blood urea and triglyceride level were considered treatment related. There were no treatment related changes in other clinical chemistry parameters at any dose level in either sex.

Table 6. Clinical chemistry

	0 ppm		280 ppm		1400 ppm		7000 ppm	
week	53	104	53	104	53	104	53	104
UREA [nmol/l]								
males	9.97	12.69	10.91	13.29	11.08	15.98	12.03**	14.31
f	9.87	12.36	10.48	13.10	9.77	14.05	9.81	14.04
TRIGL [nmol/l]								
males	2.07	2.82	2.69	2.50	2.80	2.87	3.50**	2.44

* $P \leq 0.5$ % significance level ** $p \leq 0.01$

F. Urinalysis - not performed.

G. Sacrifice and Pathology:

1. Organ weight -

Organ weight data are presented in Table 6. At 52 weeks, male mice at 1400 and 7000 ppm showed decreased absolute and relative kidney weights, but absolute and relative liver weights were increased at 7000 ppm. At 104 weeks, male mice at the 1400 and 7000 ppm dose levels had decreased absolute ($p < 0.05$) and relative ($p < 0.01$) kidney weights, compared to controls. Both absolute and relative liver weights were higher in males at 280 ppm and above. The increased absolute and relative liver weights in males at 280 ppm were attributed to the high incidence of hepatocellular neoplasms at that dose, and not considered treatment related. However, the increase ($\geq$ 10% of controls) in the relative liver weights in both sexes at 7000 ppm, which was also accompanied by histological changes in the tissue, and considered toxicologically significant. Absolute and relative heart weights were decreased in both sexes at 7000 ppm. Female mice at 1400 and 7000 ppm had lower relative and absolute spleen weights compared to controls. Absolute and relative heart weights were lower in both sexes at 7000 ppm. The changes in spleen weight in females, and heart weight in both sexes at terminal necropsy were considered incidental as they had no accompanying histopathological change.

2. Gross pathology -

In both the control and treated groups, nodules were observed in the liver and lungs among males, and nodules in the ovaries, uterus and lymphoid organs, uterine dilatation as well as ovarian cysts were noted among females. The incidence and severity of these findings were comparable between the control and treated groups, except for liver nodules where incidence was higher in the low dose males. The increase in the incidence of liver nodules among low dose males correlated with the higher number of liver tumours in the same dose level. These changes were not considered treatment related as they showed no dose-relationship. One male at 1400 ppm, and three males at 7000 ppm had enlargement and/or discoloured liver. This change which was accompanied histopathologically by fatty change in the same dose group was considered a treatment related effect.

Table 6. Organ weights

Dose	0 ppm		280 ppm		1400 ppm		7000 ppm	
Necropsy Time	52 weeks	104 weeks	52 weeks	104 weeks	52 weeks	104 weeks	52 weeks	104 weeks
Males								
Kidney								
Rel. weight [mg/100 g bw]	1777	2022	1816	2060	1555**	1803**	1565**	1762**
Abs. weight [mg]	672	738	705	750	603	679**	582*	613**
Heart								
Rel. wt	517	577	459	580	470	546	483	532
Abs. wt.	195	210	178	210	181	205	180	184**
Liver								
Rel. weight [mg/100 g bw]	4565	5242	4737	6048*	4659	5137	5364**	5620
Abs. weight [mg]	1719	1923	1844	2210*	1823	1942	2019	1960
Female								
Heart								
Rel. weight [mg/100 g bw]	493	610	516	593	526	575	483	549*
Abs. weight [mg]	141	178	151	178	156	171	142	161*
Spleen								
Rel. weight [mg/100 g bw]	421	884	328	759	416	682*	355	649*
Abs. weight [mg]	118	258	96	229	122	201*	101	190*

Dunnett test: * significantly different from the control values at 5 % significance level; ** significantly different from control values at1 % significance level.

3. Microscopic pathology -

a) Non-neoplastic findings-

No histopathology was conducted at interim necropsy. Significant findings from microscopic examination at terminal necropsy are presented in Table 7. Increases in the incidence of fatty change in the liver were recorded at 7000 ppm, in males (42% vs 10%) and females (14% vs 4%) compared to controls. These changes were characterised by clear-cut intracellular vacuoles in single or groups of liver cells distributed in the liver parenchyma. The finding taken together with the observed higher triglyceride concentration in males at 7000 ppm were interpreted by the study author as adaptive processes and not as hepatotoxic effects. However, hepatic fatty change which was associated with increased organ weight and discolouration, as well as increased blood triglyceride levels (at 53 weeks), were considered by the reviewer as indicators of a toxic response, rather than adaptive process at that dose. Interestingly, the incidence of kidney tubular vacuolization in males was markedly decreased at 1400 and 7000 ppm compared to the controls. This effect correlated with the lower kidney weights in males. These kidney findings have been described frequently in previous long-term studies with male mice of this strain in the testing laboratory. They are of unclear toxicological relevance, and were not considered (by the study author) to manifest tissue damage. However taken in light of the concurrent increase in blood urea concentrations in both sexes, at 1400 and 7000 ppm, this change is considered by the reviewer to be indicative of treatment related restricted kidney function. No significant histological findings were observed to explain the organ weight changes observed in the spleen at 1400 and 7000 ppm, and in the heart at 7000 ppm.

Table 7 Incidence of non neoplastic histological findings.

Sex	males				females			
Dose (ppm)	0	280	1400	7000	0	280	1400	7000
number of animals	50	50	50	50	50	50	50	50
liver fatty change	5	8	5	21	2	1	4	7
kidney tubular vacuolization	50	50	24	3	0	0	0	0

b) Neoplastic changes-

The incidences of hepatic neoplasms are presented in Table 8. At 280 ppm, the incidence of hepatocellular neoplasms (adenomas and carcinomas combined) in males (50%) was higher that in the control males (28%). The increased incidence was however considered incidental because of lack of a dose-relationship at higher doses. There was also a slight increase in the incidence of liver adenomas in females at 1400 ppm and 7000 ppm (4% and 8%), but the tumour incidence was within the historical range for this strain of mice (historical control 7% to 58%). The incidence of other neoplasms was comparable between the control and treated groups.

Table 8. Incidence of selected hepatocellular neoplasms

Dose	**0 ppm**	**280 ppm**	**1400 ppm**	**7000 ppm**
No. of examined animals	50	50	50	50
Liver				
adenoma (b) **male**	7	15	7	7
female	1	1	2	4
carcinoma (m) **male**	7	10	6	7
female	2	1	1	0

(b) = benign; (m) = malignant

III. DISCUSSION

Following dietary dosing of mice with SZX 0722 technical for up to 105 week, there were no treatment-related clinical signs, nor effects on mortality. Slight increases in food and water intakes-relative to body weight gain were observed in males at males at 7000 ppm. Although the decrease in food and water consumption were marginal, similar observations were noted in the sub-chronic toxicity study in mice, where both food and water intake/kg body weight were slightly higher in males at 7000 ppm, which indicate a possibility of a toxicologically significant effect. Blood urea nitrogen concentrations were increased in both sexes at 1400 and 7000 ppm, and there was a concurrent decrease in absolute and relative kidney weights in males at the same dose, suggestive of impared kidney function. Triglyceride concentration was significantly higher in males at 7000 ppm at the interim sacrifice. At the final sacrifice, absolute and relative liver weights were higher in males at 280 ppm and at 7000 ppm, but not at 1400 ppm. The increased absolute and relative liver weights in males at 280 ppm, were attributed to the high incidence of hepatocellular neoplasms at this dose, and was not considered treatment related. However, the increase ($\geq$ 10%) in the relative liver weights in both sexes at 7000 ppm had accompanying tissue changes in the liver, hence was considered toxicologically significant. In the liver, increase in the incidence of fatty changes was observed in both

sexes mice at 7000 ppm and was considered toxicologically significant. The increases in spleen weight in females at 1400 and 7000 ppm, and heart weights in both sexes at 7000 ppm were considered incidental, because they had no accompanying histological changes.

At terminal necropsy, the incidence of tubular vacuolization of the kidney was markedly decreased in males at 1400 ppm and above. Such findings have been described frequently in long-term studies with male mice of that particular strain and were considered to be of unclear toxicological relevance. A slightly higher incidence of hepatocellular neoplasms was recorded in males at 280 ppm, compared to controls or other treated males. There was also a slightly increased incidence of liver adenomas in females at 1400 ppm and above. The incidence of hepatocellular neoplasms in both sexes was considered incidental, because of a high incidences of spontaneous hepatocellular neoplasms in this mouse strain (historical control range from 7% to 58%) and a lack of a dose-relationship.

A. Investigators' conclusions.

Under conditions of this study, administration of SZX 0722 was well tolerated without treatment related adverse effects in male mice up to 1400 ppm, and in female mice up to and including 7000 ppm. The incidence and distribution of all tumour types do not indicate a carcinogenic potential of SZX 0722 in mice. The NOAEL in males is 1400 ppm, equal to 283.4 mg/kg bw/day, based on slightly higher food and water intake and slightly lower body weights at 7000 ppm. The NOAEL for females is 7000 ppm, equal to 2544 mg/kg bw/day, the highest dose tested.

B. Reviewer comments:

SZX 0722 technical (95.8 - 98.5 %) was administered to groups of $B6C3F_1$ mice, 50/sex/dose, in the diet at concentrations of 0, 280, 1400, and 7000 ppm (equal to 0, 58.5, 283.4, and 1566.8 mg/kg bw/day for males, and 0, 97.4, 503.1, and 2544.0 mg/kg bw/day for females) for up to 105 weeks. An additional 10 animals/sex/dose were similarly treated to serve as interim sacrifices after 52 weeks. Triglyceride concentration was significantly higher in males at 7000 ppm at the interim, but not at the end of the treatment period. Male mice at 1400 and 7000 ppm showed lower absolute and relative kidney weights both at the interim and the final necropsy. In the liver, a significant increase in the incidence of fatty changes was recorded in both sexes at 7000 ppm. This finding taken together with the increased triglyceride concentration in males at 7000 ppm were interpreted by the study author, as adaptive. However, hepatic fatty change which was associated with organ weight increase, gross discolouration, and increased blood triglyceride levels was considered by the reviewer as sufficient indication of a treatment-related toxic response at that dose. At terminal necropsy, the incidence of kidney tubular vacuolization decreased in males at 1400 and above, and correlated with the lower kidney weights in males at these doses. Although such findings have been described in long-term studies with male mice of this strain at the testing laboratory, taken together with the concurrent increase in blood urea nitrogen concentrations in both sexes, these changes are considered by the reviewer to be indicative of altered kidney function. The apparent increased incidence of liver adenomas in females at 1400 ppm and above, was within the historical control range for that tumour , while slight increase in incidence of hepatocellular neoplasms only in the in low dose males lacked a dose-relationship,

hence were considered incidental. Therefore, there was no evidence of a treatment-related effect on tumour incidence for this compound.

The LOAEL in both sexes was 1400 ppm (283.4 and 503.1 mg/kg bw/d in males and females, respectively), based on increased blood urea nitrogen concentrations in both sexes and decreased kidney weights in males, as well as decreased tubular vacuolization in kidney of males at that dose and above.

The NOAEL in both sexes was 280 ppm. (58.5 and 97.4 mg/kg bw/d in males and females, respectively).

SZX 0722 technical was not carcinogenic in mice under conditions of this study.

C. Study deficiencies

There were no deficiencies that would affect the acceptability of this study.

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Table 6 - Mortality - Main Groups

Mortality Main Groups								
Dose (ppm)	0	280	1400	7000	0	280	1400	7000
Sex	m	m	m	m	f	f	f	f
n	50	50	50	50	50	50	50	50
days								
1 - 90	0	0	0	0	0	0	0	0
1 - 180	0	0	0	0	0	0	0	1
1 - 270	0	1	0	0	0	0	0	1
1 - 360	0	1	1	0	1	0	2	1
1 - 450	0	2	1	0	1	1	3	4
1 - 540	0	2	1	0	3	1	4	6
1 - 630	1	2	2	3	7	5	5	10
1 - 720	8	6	4	8	17	14	13	14
1 - 746	8	6	6	8	18	19	13	18
%	16	12	12	16	36	38	26	36

Table 7 - Mortality - Satellite Groups

Mortality Satellite Groups								
Dose (ppm)	0	280	1400	7000	0	280	1400	7000
Sex	m	m	m	m	f	f	f	f
n	10	10	10	10	10	10	10	10
days								
1 - 90	1	0	0	1	0	0	0	1
1 - 180	1	0	0	1	0	0	0	1
1 - 270	1	0	0	1	0	0	0	1
1 - 360	1	0	0	1	0	0	0	1
1 - 365	1	0	0	1	0	0	0	1
%	10	0	0	10	0	0	0	10

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Table 8 - Body Weights (g)

Sex	m	m	m	m	f	f	f	f
Dose (ppm)	0	280	1400	7000	0	280	1400	7000
Week								
0	20.6	21.4 ++	20.6	20.2	16.6	17.1 +	17.2 ++	17.0
1	21.4	21.3	21.3	21.2	17.7	17.8	17.3	17.2 +
2	22.3	22.1	22.1	22.0	18.5	18.7	18.4	18.1
3	22.8	22.6	22.6	22.6	18.8	19.2	18.9	18.6
4	23.3	23.1	23.1	22.8	19.4	19.6	19.5	19.1
5	24.0	23.8	23.8	23.3 +	20.0	20.3	20.1	19.9
6	24.6	24.4	24.3	23.8 +	20.7	21.2 +	20.7	20.6
7	25.3	25.0	24.8	24.5 +	21.1	21.6 +	21.3	21.2
8	25.2	25.1	25.2	25.1	21.5	21.7	21.6	21.4
9	25.6	25.8	25.9	25.2	21.8	22.2	22.2	21.9
10	26.1	26.5	26.4	25.6	22.1	22.7	22.6	22.5
11	26.6	27.1	27.0	26.3	22.6	22.9	22.9	23.0
12	27.1	27.8	27.7	26.7	23.1	23.4	23.2	23.1
13	27.6	28.1	27.9	27.2	23.1	23.7	23.5	23.5
17	30.2	30.9	31.1	29.7	24.1	24.5	24.1	23.7
21	31.4	32.1	32.9 +	30.7	24.7	25.1	24.9	24.3
25	32.4	33.7	34.6 ++	31.5	25.2	25.8	25.7	25.0
29	34.9	36.0	36.7 +	34.5	27.2	27.5	27.0	26.8
33	37.3	38.1	38.4	36.6	28.1	29.2	28.6	28.2
37	37.1	37.4	38.1	36.0	27.6	28.5	28.4	28.2
41	37.6	38.4	38.4	36.5	28.1	29.1	28.8	28.7
45	37.5	38.1	38.1	35.9	28.4	29.8	28.5	28.6
49	38.6	38.8	39.0	37.0	29.0	29.5	29.3	28.6
53	38.6	38.7	39.3	36.8	29.2	29.8	29.6	28.9
57	39.2	39.7	40.3	37.4	29.6	30.1	30.2	28.8
61	39.3	39.6	39.8	37.8	29.7	30.8	30.6	29.9
65	38.5	38.9	39.6	37.5	29.8	30.8	31.0	30.5
69	39.3	39.4	40.1	37.5	29.9	30.9	31.6	30.5
73	39.8	39.8	40.4	37.0 +	30.4	31.1	32.0	30.1
77	39.7	39.4	40.4	37.4	30.3	31.0	31.6	30.0
81	38.5	37.7	39.1	35.9 +	30.5	30.5	30.4	29.2
85	38.7	37.9	39.1	36.2	29.9	30.4	30.7	29.5
89	37.4	36.9	38.1	34.9	29.4	30.1	29.5	28.8
93	37.4	36.7	37.5	34.3 +	29.2	29.7	29.0	29.2
97	36.8	36.5	37.3	34.6	28.9	29.9	28.9	28.7
101	36.1	36.1	36.9	34.0	28.5	29.6	28.8	28.5
105	36.0	35.9	37.5	34.3	29.1	29.9	29.4	28.8

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